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Letter to the Editor

Familial Heterotaxia: What Is the Inheritance in This Family?

To the Editor:

Recently, Alonso and colleagues [1995] reported on a number of cases of autosomal dominant heterotaxia in the *American Journal of Medical Genetics*. We would like to report a case of familial heterotaxia whose inheritance is unclear.

II-2 and II-3 are sisters married to men who are related neither to themselves nor to each other.

III-1 was diagnosed on antenatal ultrasonography as having complex congenital heart disease. Foetal blood sampling was carried out and was normal (46,XX). Postnatally she was found to have a complete atrioventricular septal defect, separate apical VSD, small left ventricle, interrupted inferior vena cava, hypoplastic aortic arch, and aortic coarctation. The child developed necrotising enterocolitis on day 2 and died at age 11 days. Autopsy confirmed these findings; the abdominal organs were all in their normal sites with a single spleen of normal size.

III-3 was found on 18-week ultrasound to have severe congenital heart disease and the pregnancy was terminated. Autopsy showed left atrial isomerism with a large atrial septal defect and a single ventricle with a single ventricular outflow tract. There was absent lobation of the right lung. The stomach was located on the right, the liver was midline, as was the gallbladder. The spleen was in its correct position and was of normal size for gestation. The whole large intestine lay in the right side of the abdomen.

III-4 had the diagnosis of interrupted inferior vena cava and right stomach made on antenatal ultrasound study. Postnatally he was found to have a midline liver, absent gallbladder, biliary atresia, and confirmation of the antenatal findings. The biliary atresia was managed by the Kasai procedure on day 20. He has polysplenia. Cardiac situs and anatomy is normal. His karyotype is 46,XY.

II-2 and II-3 have normal cardiac situs clinically and on chest radiograph. II-3 has normal abdominal situs on abdominal ultrasound. This of course does not exclude the possibility of subtle signs of heterotaxia. Both II-2 and II-3 have normal karyotypes (46,XX).

The mode of inheritance of heterotaxia in this family is unclear. Possibilities include the following:

1. Autosomal dominant with no discernible expression in obligate carriers (II-2 and II-3). The pedigree is similar to family 2 in Alonso et al. [1995].
2. Autosomal recessive. This is unlikely given the rarity of the condition and the absence of consanguinity.
3. Mitochondrial mutation. This is possible given the maternal inheritance. Heterotaxia has not previously been described in conditions due to mitochondrial mutations.
4. A cryptic chromosomal translocation. The normal developmental progress of III-4 makes this unlikely.
5. Paternally imprinted gene mutation such that the condition is expressed in the offspring of the females who carry the mutation but is not expressed in themselves. This is analagous to the proposed mechanism of familial Angelman syndrome [McKusick, 1994].

Autosomal dominant heterotaxia was described by Niikawa and colleagues [1983] and Alonso and colleagues [1995]. Apparent autosomal recessive heterotaxia is more common, but most cases appear to be sporadic [McKusick, 1994]. X-linked laterality sequence is also well described [Mathias et al., 1987] and linkage has been demonstrated to Xq24- q27.1 [Casey et al., 1993]. Recently Britz-Cunningham and coworkers [1995] demonstrated homozygous mutations in the *con-*

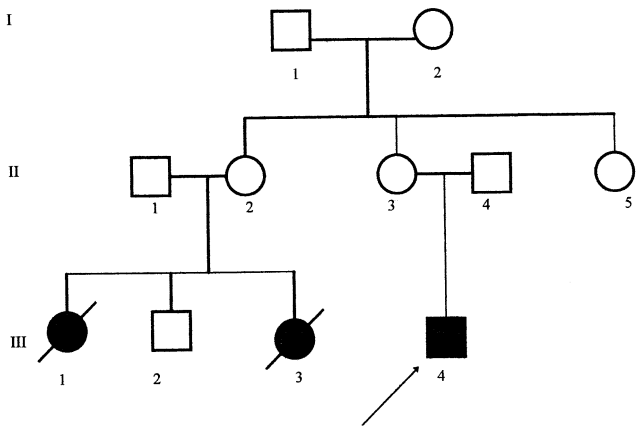

Fig. 1. Pedigree of the family described in the text.

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nexin43 gap junction gene in patients with defects of laterality.

It is possible that at least some cases of "sporadic" heterotaxia in fact represent new dominant mutations, and as more people with this condition survive, more second-generation occurrence will be seen.

REFERENCES

Alonso S, Pierpont ME, Radtke W, Martinez J, Chen S-C, Grant JW, Dahnert I, Taviaux S, Romey M-C, Demaille J, Bouvagnet P (1995): Heterotaxia syndrome and autosomal dominant inheritance. Am J Med Genet 56:12–15.

Britz-Cunningham SH, Shah MM, Zuppa CW, Fletcher WH (1995): Mutations of the connexin43 gap-junction gene in patients with heart malformations and defects of laterality. N Engl J Med 332:1323–1329.

Casey B, Devoto M, Jones KL, Ballabio A (1993): Mapping a gene for familial situs abnormalities to human chromosome Xq24-q27.1. Nature Genet 5:403–407.

Mathias RS, Lacro RV, Jones KL (1987): X-linked laterality sequence: Situs inversus, complex cardiac defects, splenic defects. Am J Med Genet 28:111–116.

McKusick VA (1994): "Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders." 11th ed. Baltimore: Johns Hopkins University Press.

Niikawa N, Kohsaka S, Mizumoto M, Hamada I, Kajii T (1983): Familial clustering of situs inversus totalis and asplenia and polysplenia syndromes. Am J Med Genet 16:43–47.

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